Blocking RAN translation without altering repeat RNAs rescues C9ORF72-related ALS/FTD phenotypes

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C9ORF72 repeat expansion is the most common genetic cause of amyotrophic lateral sclerosis and frontotemporal dementia. Toxicity is thought to result from accumulation of either repeat RNAs and/or dipeptide repeat proteins (DPRs) translated from G_4C_2-containing transcripts. To disentangle RNA from DPR toxicity, we mutated a CUG codon predominantly used to initiate DPRs translation from all three reading frames. This mutation disrupted DPR synthesis while preserving expression of repeat-containing RNAs. Behavioral deficits and pathological abnormalities, including neuroinflammation, p-TDP-43 inclusions, increased neurofilament levels, and motor neuron loss were alleviated in *C9ORF72* mice despite accumulation of RNA foci. Base editing of the CUG codon into CCG also improved phenotypes and cell survival in patient iPSC-derived neurons, highlighting the potential of therapeutically targeting DPR production rather than repeat RNAs.

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